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Short communication

First aromatic ring acetamidation by anodic oxidation

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ABSTRACT

Anodic oxidation of 1-(trifluoromethyl)benzene in dry acetonitrile/Bu₄NBF₄ under constant potential conditions led to 2-(trifluoromethyl) acetanilide in 86% yield. Other experimental conditions, as the use of constant current or the change in the supporting electrolyte were considered.

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1. Introduction

Trifluoromethylated arenes are important motifs in many pharmaceuticals, agrochemicals and organic materials due to the strong electron-withdrawing nature and the large hydrophobic domain of a CF₃-group [1,2].

The interest of acetamidated 1-(trifluoromethyl)benzene deals notably with the utility of the acetamido group providing other opportunities to transform it into different functional groups, opening new access to many synthetic therapeutic agents [1,3,4].

Conventional preparations of these acetamidated 1-(trifluoromethyl)benzenes have been recently described, as the Pd(II)-catalyzed trifluoromethylation of the aromatic C–H bond in acetanilides, which provides the highly biological potential key structure of ortho-CF₃ acetanilides [5] or the ortho-trifluoromethylation of N-aryl-benzamide catalyzed by Pd using the Umemoto reagent as the CF₃ source [6]. Direct Cu-catalyzed trifluoromethylation of pivalamido arenes with Togni reagent takes place with high selectivity at the ortho-position [7].

On the other hand, the metabolism of 2-trifluoromethylacetanilide in the rat has been determined [8].

The electrochemical acetamidation reaction of alkyl aromatic compounds (arenes) was studied in depth by Eberson et al. [9] in acetonitrile/alkaline perchlorate at a platinum anode. The accepted mechanistic proposal [10] is the aromatic ring oxidation in a 2e[−]/substrate molecule process, followed by a Ritter-type reaction with further

hydrolysis of the generated cation during the work-up, to produce the corresponding side-chain acetamide, as indicated in Scheme 1.

As far as we know aromatic ring anodic acetamidation has never been achieved; once the anodic discharge was displayed, the target of acetonitrile has been always the side aliphatic chain. In 2008 and 2011, Kumar et al. [11] published two articles describing the electrochemical ring acetamidation of aromatic compounds using a 0.1 M solution of starting material in acetonitrile (25 mL)/water (25 mL)/KCl 0.1 M as a solvent and supporting electrolyte (SSE). We have tried to reproduce these results, under their experimental conditions, with acetophenone [11a] and p-xylene [11b] as substrates. We have not observed any acetamidation of acetophenone. Instead, the expected benzoic acid was obtained as the main product. In the case of p-xylene, these authors reported a 97% yield of 2,5-dimethyl acetanilide. In this case we have found some aliphatic acetamidation but none of the mentioned aromatic acetamidation.

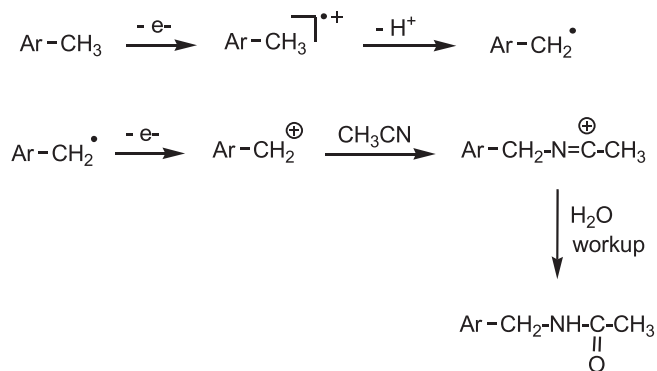
In the present communication we describe for the first time an aromatic acetamidation reaction at the electrode.

2. Experimental section

The electrolyses were carried out using an Amel potentiostat Model 552 with electronic integrator Amel Model 721. Mass spectra (EI, ionizing voltage 70 eV) were determined using a THERMOFISHER ITQ-900 DIP/GC-MSn mass-selective detector. IR spectra of the compounds were recorded as dispersions in KBr or NaCl films on a Perkin-Elmer FT-IR spectrometer Spectrum 2000. ¹H and ¹³C NMR spectra were recorded in CDCl₃ on Varian Unity 300 (300 MHz) spectrometer with tetramethylsilane (TMS) as the internal standard. The chemical shifts

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Scheme 1. Accepted mechanistic proposal in the electrochemical arene acetamidation.

are given in ppm. Melting points were measured on a Reichert Thermovar microhot stage apparatus and are uncorrected.

2.1. General electrochemical procedure

1-(Trifluoromethyl)benzene (**1**) (5.10^{-3} mol, 0.73 g) was dissolved in 60 mL SSE: anhydrous acetonitrile/ Bu_4NBF_4 (0.05 M) and electrolyzed in a concentric and divided cell (glass-frit D4-diaphragm) equipped with a magnetic stirrer under constant potential conditions (+2.8 V, vs Ag/AgCl(sat)) at temperature of 18 °C maintained constant with a cryostat. A platinum plate (10 cm^2) was used as working and counter electrode and a Ag/AgCl (sat) electrode as the reference.

Once the reaction was finished, the solvent in the anodic solution was removed under reduced pressure. The residue was extracted with ether/water and the organic phase dried over Na_2SO_4 and concentrated by evaporation. The resulting solid was chromatographed on silica gel 60 (35–70 mesh) in a (22 × 3 cm) column, using CH_2Cl_2 :EtOH (20:1) as eluent. Spectroscopic data of the obtained compounds are given below.

2-(Trifluoromethyl)acetanilide (**2**): (870 mg, 86% yield). Mp 96 °C. [Lit. [12] 96–96.5 °C]. IR(KBr) $\nu = 3286, 3037, 2962, 1674, 1531, 1320, 1125, 1036, 764 \text{ cm}^{-1}$. ^1H NMR (300 MHz, CDCl_3) δ : 2.15(s, 3H), 7.16 (t, 1H, $J = 7.5 \text{ Hz}$), 7.36 (bs, 1H), 7.49 (t, 1H, $J = 7.8 \text{ Hz}$), 7.54 (d, 1H, $J = 7.5 \text{ Hz}$), 8.08 (d, 1H, $J = 7.8 \text{ Hz}$). ^{13}C NMR (75.4 MHz, CDCl_3) δ : 24.6, 122.2, 124.5, 124.7, 125.8, 126.0, 132.8, 135.1, 168.4. MS m/e (relative intensity) EI: 203(M^+ , 18), 184($\text{M}^+ - 19$, 3), 161(98), 141(100), 114(46), 75(5), 63(9).

3-(Trifluoromethyl)acetanilide: Mp 102 °C. [Lit. [13] 100–102 °C]. MS m/e (relative intensity) EI: 203(M^+ , 17), 184($\text{M}^+ - 19$, 9), 161(100), 142(10), 114(12), 63(9).

3. Results and discussion

When 1-(trifluoromethyl)benzene (**1**) was exposed to the experimental oxidative conditions described above, using acetonitrile as the solvent (it means with a weak nucleophile), it was transformed into the corresponding 2-(trifluoromethyl)acetanilide (**2**) in very good yield.

The reason why the alkyl aromatic derivatives afford the side chain acetamidation reaction, instead of the ring acetamidation (see Scheme 1), is that the initially electrogenerated cation radical at the ring, due to the weak nucleophilic character of acetonitrile, loses an aliphatic proton to produce the more stable benzyl radical that is further oxidized to the cation and subsequently attacked by the acetonitrile through a Ritter-type reaction.

However, when anodic acetoxylation is performed, substitution at the aromatic ring or at the aliphatic side chain can occur depending on the SSE employed. The use of weak nucleophile solvent-supporting electrolyte systems such as $\text{HOAc}/\text{NaClO}_4$ drives the reaction to the aliphatic acetate [14], however when the SSE contains a stronger nucleophile: HOAc/NaOAc the obtained product is the arylacetate [15] because once the aromatic cation radical is formed the acetate as nucleophile attacks the ring before any side chain proton is evolved.

The preparative-scaled electrolysis of (**1**), when carried out under our best experimental conditions, allowed getting the aromatic ring acetamidation product (**2**), after a charge consumption corresponding to a theoretical $2e^-$ /substrate molecule process. Once finished and further elaborated (**2**) was obtained in 86% yield together with a 10% mixture of 3-(trifluoromethyl)acetanilide and 4-(trifluoromethyl)acetanilide in a 3:1 respectively relationship determined by GC and ^1H -NMR.

Concerning the mechanism proposal that explains the formation of (**2**), it is summarized in Scheme 2.

After the first electron transfer to the anode, the cation radical cannot be further stabilized by loss of a fluorine cation, as in the case of alkyl aromatic substrates that evolve, as already Ebersson described, leaving a proton. Now the Ritter-type reaction with the solvent, acetonitrile, takes place at the ring.

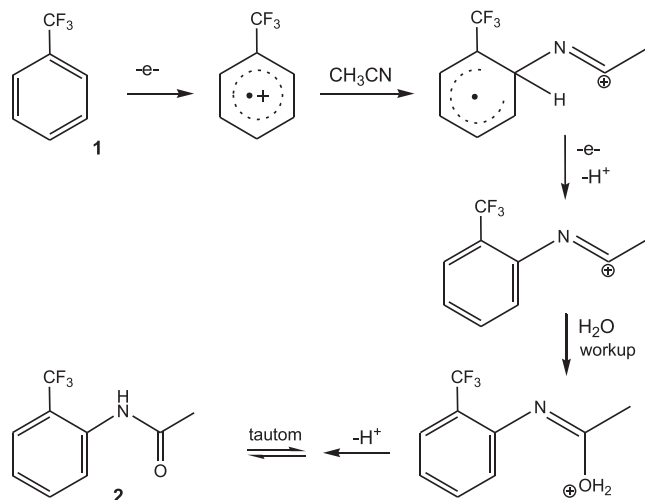
The 2-(trifluoromethyl)acetanilide (**2**) is the major isomer because the strong withdrawing inductive effect of the trifluoromethyl substituent makes charge deficient the adjacent positions, more easily to be attacked by nucleophiles.

It is important to notice that the best results were obtained using Bu_4NBF_4 as electrolyte. When it was substituted by LiClO_4 , under the applied potential conditions, aromatic chlorinated products were obtained and the reaction was dirty.

When the electrolysis was performed under constant current conditions (300 mA applied during 1 h) while maintaining identical the rest of the reaction parameters, the yield of 2-trifluoroacetanilide was 54%. This lower yield is due to the competing formation of some monoacetamide dimers through coupling of the trifluoromethyl benzene cation radical, in addition to the 3- and 4-trifluoroacetanilide isomers.

4. Conclusions

The anodic discharge of (trifluoromethyl)benzene under constant potential conditions of +2.8 V (vs Ag/AgCl (sat)) and acetonitrile/ Bu_4NBF_4 as SSE, provides the first example of high yielded aromatic ring acetamidation.



Scheme 2. Aromatic ring acetamidation mechanism.

The methodology described herein to get trifluoromethylated acetanilides could be easily scaled up under constant current conditions and opens a new access to biological and therapeutic agents.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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